Not Another Formula for Heart Rate Correction of QT Interval

Peter J. Bourdillon, M.B.B.S., F.R.C.P.

ECG Department, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, U.K.

Background: Normal limits for QT and heart rate were developed in a Japanese population undergoing 24 hour recordings of the electrocardiogram (ECG). The purpose of this study is to validate these normal limits in a West London population having 12-lead ECGs.

Methods: A retrospective observational cohort of 10,099 patients aged 20–79 attending a hospital ECG department was studied. From the Japanese data z-scores were calculated for men under 50, for men over 50, for women under 50 and for women over 50. z-scores were used to compare the West London and Japanese populations.

Results: Cardiac infarction injury scores (CIIS) for all four groups were less than zero indicating a population at low risk of cardiovascular disease. From the Japanese data a z-score of 1 is roughly 20 ms. West London mean (SD) z-scores for men under 50, for men over 50, for women under 50 and for women over 50 were 0.20 (0.85), –0.02 (0.86), 0.14 (0.93), and –0.45 (0.88), respectively.

Conclusions: The distributions of the QT and heart rate data of a West London population at low risk of cardiovascular disease are comparable to the Japanese data. The Japanese QT normal limits for women over the age of 50 are about 9 ms higher regardless of heart rate. The QT normal limits for Afro-Caribbeans are about 5 ms lower than other ethnic groups. The Japanese normal limits are applicable elsewhere, albeit adjusting for women over the age of 50 and for Afro-Caribbeans.

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QT interval; z-score; normal limits; cardiac infarction injury score

Both long and short heart rate-corrected QT intervals are associated with an increased risk of sudden death.^{1,2} The QT interval–heart rate relationship shows both inter- and intra-individual variability.^{3–5} That 20 formulae⁶ for determining the relationship between QT interval and heart rate have been described implies that finding a formula that is independent of heart rate is probably unrealistic.

In 2006 Sugao et al.⁷ recorded 24 hour electrocardiograms (ECGs) and measured the QT interval and the heart rate every 15 seconds in 422 Japanese subjects. From the data the authors derived normal limits of QT interval at different heart rates, thereby obviating the need for a QT-heart rate correction formula. Sugao et al. described normal limits for four categories: men under and over 50 years of age, and women under and over 50 years of age. The purpose of the present study is to validate these normal limits in a West London population of more than 10,000 subjects using 12-lead electrocardiogram.

raphy. Should the normal limits be valid, then the statistical techniques used in this article would simplify the analysis of 24 hour ambulatory monitoring of QT interval.

METHODS

Sugao et al.⁷ recorded 24 hour ECGs in 422 Japanese hospital subjects without apparent cardiovascular disease. They sampled the QT interval and heart rate at 15 second intervals and obtained the means and standard deviations of QT at heart rates between 45 and 120 beats per minute (bpm) at 5 bpm intervals for men and women under and over 50 years of age. In this study, the data of Sugao has been extended as follows.

- Calculation of z-scores⁸: (measured QT – (heart rate-, age- and gender-adjusted QT mean))/(heart rate-, age- and gender-adjusted QT standard deviation).

Address for reprints: Peter J. Bourdillon, M.B.B.S., F.R.C.P., ECG Department, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, W12 0HS, U.K. Fax: +442083833952; E-mail: pbourdillon@msn.com

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- Linear interpolation to calculate z-scores for heart rates between 50 and 95 bpm.

The population used to validate the Sugao data consisted of a consecutive series of different patients aged 20–79 years attending the ECG department of the Hammersmith Hospital in West London between April 2002 and May 2006. All 12 lead ECGs were interpreted by the GE-Marquette 12SL version 235 program. Patients were included if first, the reported rhythm was either sinus rhythm, sinus arrhythmia or sinus bradycardia, second, the heart rate was between 45 and 100 bpm and third, no contour abnormality was present. The program's original report was used: no editing of the program's measurements or reports was undertaken although measurements more than three SDs from the mean were inspected. A program was written to extract and store the measurements. The cardiac infarction injury score (CIIS)⁹ was calculated for each subject to assess the risk of cardiovascular disease in the population.

From the West London data the means and standard deviations of QT interval at heart rates between 45 and 100 bpm at 5 bpm intervals for men and women under and over 50 years of age were calculated. Linear interpolation was used to calculate z-scores for all heart rates between 50 and 95 bpm.

Four QT—heart rate correction formulae were compared with the Sugao data, viz. Bazett,¹⁰

Sagie,¹¹ Fridericia,¹² and Rautaharju and Zhang.¹³ Each correction formula was "forced" to pass through the Sugao QT value at the heart rate of 60 bpm taking into account gender and age. The number of Sugao SDs from the Sugao mean was calculated for heart rates 52.5, 57.5, 62.5, 67.5, 72.5, 77.5, 82.5, 87.5, and 92.5 for each gender and age combination, i.e., 36 SD measurements for each QT correction formula.

Statistical Analyses

Comparison between the z-scores of Afro-Caribbeans and of others was undertaken using the unpaired *t*-test. Comparison of Sugao data with QT—heart rate correction formulae was undertaken by determining which formula had the smallest mean and standard deviation of Sugao SDs. Linear Multiple Regression Analysis to determine the contribution of age, gender and ethnicity to z-scores and CIIS values was undertaken using StatsDirect version 2.3.2 (www.StatsDirect.com).

RESULTS

The 12-lead ECGs of 10,099 patients aged between 20 and 79 years with heart rates between 50 and 95 bpm were analysed.

Table 1 shows their demographics and the corresponding z-scores. The key features are as follows.

Table 1. The Number of Subjects in each of Four Groups Together with their z-scores and CIIS Values

Ethnicity	Under 50			Over 50		
	Number	z-score Mean (SD)	CIIS Mean (SD)	Number	z-score Mean (SD)	CIIS Mean (SD)
Men						
White	1151	0.26 (0.85)	−3.70 (7.00)	1578	0.05 (0.84)	−1.07 (7.67)
Afro-Caribbean	185	−0.09 (0.83)	−4.81 (6.44)	137	−0.37 (0.86)	−2.79 (6.98)
South Asian	358	0.18 (0.81)	−2.65 (6.73)	419	−0.09 (0.87)	−0.44 (7.34)
Oriental	126	0.12 (0.86)	−2.39 (7.39)	97	−0.08 (0.90)	−0.95 (7.85)
Other	74			72		
Total	1894	0.20 (0.85)	−3.54 (6.97)	2303	−0.02 (0.86)	−1.08 (7.57)
Women						
White	1541	0.19 (0.90)	−2.39 (6.75)	2199	−0.44 (0.89)	−1.15 (7.40)
Afro-Caribbean	502	−0.11 (0.94)	−4.81 (7.17)	334	−0.61 (0.86)	−3.79 (7.65)
South Asian	427	0.11 (0.85)	−2.06 (6.70)	426	−0.38 (0.88)	−0.63 (7.63)
Oriental	169	0.40 (1.07)	−2.57 (7.40)	106	−0.45 (0.73)	−2.41 (7.00)
Other	118			80		
Total	2757	0.14 (0.93)	−2.80 (6.95)	3145	−0.45 (0.88)	−1.42 (7.49)

1. The means of the z-scores, apart from the women over the age of 50, are near to zero indicating close agreement with the Japanese data.
2. The mean difference of 0.45 in the z-scores in Japanese women over the age of 50 and those in the West London population is equivalent to a difference in QT interval of 9 ms regardless of heart rate.
3. Afro-Caribbeans have lower z-scores than those from other ethnic groups. Comparing the z-scores of all 1158 Afro-Caribbeans with the other 8941 patients the difference is 0.25 ($P < 0.0001$, 95% CI 0.19–0.30), a QT difference of approximately 5 ms regardless of heart rate.
4. The mean CIIS values are all less than zero, with SDs less than 8, indicating a population at low risk from cardiovascular disease.
5. Afro-Caribbeans have lower CIIS values than those from other ethnic groups.
6. South Asians have higher CIIS values than those from other ethnic groups.

Figure 1 shows the QT intervals and corresponding heart rates of the ECGs of 1894 men under 50, 2303 men over 50, 2757 women under 50, and 3145 women over 50 plotted together with the Sugao upper and lower normal limits (mean $\pm$ 2 SD).

On multiple regression analysis the z-score of the men was 0.24 ($t = 13.4$, $P < 0.0001$) less than that of the women, the z-score of those under 50 was 0.45 ($t = 25.4$, $P < 0.0001$) less than that of those over 50 and the z-score of the Afro-Caribbeans 0.27 ($t = 9.8$, $P < 0.0001$) less than that of other ethnic groups. Also on multiple regression analysis, the CIIS value of those over 50 was 1.71 ($t = 11.8$, $P < 0.0001$) higher than those under 50, the CIIS value of women was 0.32 ($t = 2.15$, $P = 0.031$) higher than men, the CIIS value of the Afro-Caribbeans was 2.12 less ($t = 9.2$, $P < 0.0001$) and the CIIS value of the South Asians 0.63 more ($t = 3.2$, $P < 0.002$) than that of other ethnic groups.

The difference in the mean (SD) of the Sugao standard deviations between Sugao and QTcBazett was -20.3 (0.63), between Sugao and

Figure 1. QT-heart rate plots of ECGs recorded from hospital subjects that were analysed by the GE-Marquette SL-12 program and which were reported as having a normal contour and either sinus rhythm, sinus arrhythmia or sinus bradycardia. The top left panel shows men under 50, the top right men over 50, the bottom left women under 50 and the bottom right women over 50. The lines are the upper and lower limits of normal (mean $\pm$ 2 SD) of Sugao et al.⁷

QTcFridericia was -0.8 (0.16), between Sugao and QTcFramingham was -1.0 (0.17), and between Sugao and QTcRautaharju was -12.1 (0.42). These results indicate that the shapes of the curves of the four sets of Sugao means are almost identical to the QTcFridericia—heart rate and QTcFramingham—heart rate curves.

DISCUSSION

Knowing the means and standard deviations of QT at different heart rates of a healthy population, the number of standard deviations a particular QT—heart rate combination is away from the mean for that heart rate can be determined. The data of Sugao et al. provide us with the means and standard deviations of QT at different heart rates. Their data were obtained from 24-hour ECG recordings of a hospital population of 422 Japanese without apparent heart disease. By sampling at 15 second intervals their data is based on approximately 2 million samples. The number of standard deviations from the mean is the z-score and we have described this QT "correction" factor as the Sugao-derived z-score. Sugao et al. derived normal limits for four groups: men under the age of 50, men over 50, women under 50 and women over 50.

The Sugao-derived z-score has been validated in a consecutive series of ECGs recorded in a hospital population in West London. The QT and heart rate measurements obtained from a commercial program for interpreting the ECG were used: for inclusion the rhythm of the ECGs had to be either

sinus rhythm, sinus arrhythmia or sinus bradycardia and the contour of the complexes had to be reported as normal. The four panels of Figure 1 show how well the West London data fit with the Japanese data. Above heart rates of 80 bpm the fits are not so good as below 80 bpm. Table 2 shows that the standard deviations of the West London QT intervals decreased as the heart rate increased; in contrast, the standard deviations of Sugao's data change little with heart rate as can be seen from the near parallel lines in the panels of Figure 1. The less good fit above 80 bpm may be because automated single lead analysis of 24-hour ECG recordings, as was used in the Japanese study, is more subject to error in the determination of the end of the T wave than is the simultaneous measurement of 12 leads. The measurement error is commonly due to superimposition of the next P wave on the T wave. That Sugao et al. did not take into account the time the QT interval takes to adjust to abrupt changes in heart rate (QT hysteresis) is another possible explanation.¹⁴

A particular advantage of using z-scores for the QT—heart rate relationship is that there is no need to "correct" to a heart rate of 60 bpm. The use of z-scores in medicine is limited. The best known example of their routine use is in the measurement of bone densitometry, but they are also used to compare the growth of children at different ages. Another advantage z-scores have is that, because they are standard deviations and standard deviations are normally distributed, disparate groups can be aggregated and easily compared with other

Table 2. The Means and Standard Deviations (SD) of QT Intervals of the West London Population Subdivided by Heart Rate in bpm, by Gender, and by Age-Group

Heart Rate	Women				Men			
	Under 50		Over 50		Under 50		Over 50	
	Number	Mean (SD)	Number	Mean (SD)	Number	Mean (SD)	Number	Mean (SD)
45–50	48	443.4 (21.8)	82	450.5 (20.1)	80	431.3 (19.7)	97	441.0 (22.6)
50–55	127	429.9 (21.8)	207	434.9 (20.8)	145	416.6 (21.1)	204	427.9 (20.6)
55–60	232	418.2 (18.6)	396	423.3 (19.6)	248	406.8 (19.0)	268	413.3 (20.0)
60–65	387	405.2 (18.2)	516	409.1 (19.3)	319	393.6 (16.8)	416	402.7 (17.7)
65–70	483	396.6 (17.4)	552	398.8 (18.0)	318	385.0 (15.5)	429	392.5 (17.3)
70–75	473	386.4 (16.2)	472	389.5 (17.3)	283	376.9 (14.5)	331	382.7 (17.1)
75–80	415	379.8 (14.7)	407	380.8 (16.5)	239	369.6 (16.3)	244	374.7 (16.4)
80–85	306	368.4 (15.2)	264	371.1 (15.1)	157	361.6 (14.5)	188	367.2 (14.4)
85–90	227	363.9 (14.7)	197	364.6 (14.3)	101	355.3 (15.4)	146	357.6 (14.8)
90–95	107	355.4 (13.3)	134	356.3 (14.3)	84	352.6 (14.6)	77	354.5 (12.9)
95–100	86	348.3 (13.3)	86	348.2 (13.4)	50	345.0 (14.7)	49	343.3 (14.4)

Figure 2. Two graphs of a subject's QT—heart rate data analysed every minute for 48 hours. The left hand panel shows QT interval plotted against heart rate; the continuous lines showing the Japanese upper and lower limits of normal. The right hand panel shows the same data with z-score plotted against time. Nine percent of the points are below the lower limit of normal (z-score of -2) indicating an intermittent short QT interval. The lengthening of QT interval at night regardless of heart rate is demonstrated in the right hand panel. To minimize the effect of QT hysteresis the heart rate for each data point has been measured over 130 seconds but the QT interval only over the last 10 seconds. Data points were excluded if the coefficient of variation (SD/mean) of RR interval was greater than 0.125 over the 130 seconds. Ventricular ectopic and postectopic complexes were excluded.

groups as in this study: the z-scores of all the Afro-Caribbeans, regardless of gender and age, were compared with the z-scores of all other ethnic groups using an unpaired *t*-test and found to be approximately 5 ms shorter. This is consistent with the previous finding of a shorter Bazett-corrected QT in Afro-Americans than in whites.¹⁵ However, a longer QT was not found in the South Asians as was found by Rautaharju et al.¹⁶ Simplification of the analysis of QT interval data using z-scores is applicable both to 12-lead ECGs and to 24-hour ambulatory ECGs that are recorded during pharmaceutical studies. Figure 2 shows a graph of QT interval and heart rate analysed every minute for 48 hours in the left hand panel and the corresponding data plotted as z-score versus time in the right hand panel. Had the West London data been used to construct the normal limits, the proportion of measurements showing a short QT interval would have increased from 9% to 22%.

Recognising that no QT—heart rate correction formula (QTc) is independent of heart rate, it is possible to test how similar the Sugao QT—heart rate curves are to QTc—heart rate curves. This has been done by assuming each QTc formula passes through the Sugao mean value of QT interval at a heart rate of 60 bpm taking into account gender and age. The calculations indicate that the Sugao curves are virtually identical to the QTcFridericia—heart rate curves and also to the QTcFramingham—heart

rate curves. The implication is that QTcFridericia, QTcFramingham, and Sugao z-scores have similar residual variations in QT interval that are related to heart rate.

Richardson et al.¹⁷ recommended that a cardiac damage score should be calculated as part of all computerized ECG interpretations. They found that CIIS outperformed other ECG classifications determining prognosis that they studied. The means of the CIIS values in all four groups in this study indicate that each has a low risk of cardiovascular disease. Of interest are the CIIS values on multiple regression analysis of the Afro-Caribbeans, which are 2.1 lower, and of the South Asians, which are 0.6 higher, than the other ethnic groups. The low CIIS values for the Afro-Caribbeans are probably due to the tall QRS complexes they have¹⁸ while the high values in the South Asians may be related to the higher incidence of coronary artery disease in this population.¹⁹

This study demonstrates that the Japanese normal limits for the QT—heart rate relationship can be applied elsewhere, albeit adjusting for women over the age of 50 and also for Afro-Caribbeans.

Limitations of the Study

The study is validating data derived from a Japanese population in a West London population but neither study is a survey of healthy subjects

in the community. The patients in the Japanese study were recruited from a hospital population which had undergone 24-hour ECG recording: the participants had neither cardiac disease nor any other condition known to affect the QT interval. The patients in this study were those attending a hospital's ECG department. They were selected on the basis that their ECGs were reported as normal by the GE-Marquette 12SL program. Consequently, the West London population will have included patients with heart and other diseases even though they had normal ECGs. No attempt was made to change either any of the QT interval measurements or any incorrect contour statements of "normal" made by the program although measurements more than 3 standard deviations from the mean were inspected. It should be noted that the version of the program used to measure and interpret the ECGs is not as precise at measuring the end of the T wave as is the latest version.²⁰

CONCLUSIONS

The distributions of the QT and heart rate data of a West London population at low risk of cardiovascular disease are comparable to the Japanese data. The Japanese QT normal limits for women over the age of 50 are about 9 ms higher regardless of heart rate. The conversion of the Japanese data to z-scores avoids the need to use a QT interval—heart rate "correction" factor. Afro-Caribbeans have lower z-scores, equivalent to a 5 ms shorter QT regardless of heart rate, than other ethnic groups. z-scores simplify the analysis of QT interval data.

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